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MODELS FOR ANTIBODY ATTACHMENT TO VIRUS AND BACTERIOPHAGE*

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Research Report [illegible]

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1. Introduction

Several interesting mathematical problems concerned with partition into classes, and surface covering are suggested by the physical mechanisms and geometry of antibody attachment to virus particles. This paper outlines some of the recent work done in this area by Yassky (1962), myself (1962a, and b), Moran and Fazekas de St. Groth (1962) and Gilbert (1956), adds a model and other extensions of my own, and concludes with a suggestion for further investigations. I shall endeavour throughout to hold the mathematical argument at a simple level, and emphasise the model-building aspect of the work, in the hope that virologists may be tempted to use and perhaps verify experimentally some of the models put forward.

Let us consider at any time $t \geqslant 0$, a nutrient medium (either in the laboratory, or within a living animal) in which there exist a fixed number N of particles of a virus V; suppose that at time $t = 0$, $x_0 \gg N$ antibodies are released into this medium. We may expect the antibodies to attach

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themselves progressively in some random fashion to the viruses, both types of particles being subject to Brownian motion. If each virus particle permits a maximum of s attachments, then at any time $t \geq 0$, the N virus will be divided into s+1 classes consisting of $n_0(t)$, $n_1(t)$, ..., $n_s(t)$ particles with respectively 0, 1, ..., s antibodies attached to them; there will remain $x(t) = x_0 - \sum_{i=1}^{s} i\, n_i(t)$ unattached antibody particles. The $\{n_i(t)\}$ constitute a class partition of the virus particles, which varies in time t. We may, for simplicity in some cases, approximate the integer-valued random variables (r.v.'s) $0 \leq n_i(t) \leq N$, and $0 \leq x(t) \leq x_0$ by analogous functions differentiable in t; then, as we shall see, a deterministic approximation to the random evolution of the $\{n_i(t)\}$ and $x(t)$ can be found. It is also possible to obtain a stochastic approximation to the integer-valued $\{n_i(t)\}$ using the previous deterministic approximation for $x(t)$.

While such results may indicate the number of antibody attachments to the virus, they do not alone provide adequate information as to its loss of infectivity. Two cases arise, however, in which fuller information can be obtained. These are the cases when:

1) The capsule of virus V is approximately spherical, as it is for influenza; and

2) The virus V is a bacteriophage.

In Case 1, Moran and Fazekas de St.Groth (1962) have shown that the attachment of antibodies to a single approximately spherical virus particle may be formulated as a problem of geometrical probability. Consider i cylindrical antibodies in the shape of long cigars adhering by one of their ends to a particle of spherical virus; each antibody when standing normally to the virus surface shields a circular spherical cap (subtending a half-angle α at the centre of the sphere) on it from contact with a healthy cell. For the influenza virus, the radius of the sphere is 40 mμ, while the antibodies are of length 27 mμ so that the shielded area subtends a half angle $\alpha = 53.43°$. A sufficiently large number i of such antibodies would result in a complete covering of the sphere and cause loss of infectivity of the virus. Moran and Fazekas de St.Groth have obtained the asymptotic value for large i of the probability $P(i)$ that the sphere is covered by i antibodies, and more recently Gilbert (1965) has found general bounds for this probability. If at any time $t \geq 0$ we also know the partition of the N virus particles into the classes $\{n_i\}$ of particles carrying $i = 0, 1, \ldots, s$ antibodies, we can evaluate the probability of loss of infectivity of the virus at time t.

In Case 2, it is known that a single antibody attachment to the bacteriophage tail causes loss of infectivity. This means that of the s

possible attachments, a single particular one will suffice to prevent infectivity. Suppose we now partition the n_i viruses with $1 \leq i \leq s$ antibody attachments into two classes

$$0 \leq n_{1,i-1} \leq N, \quad 0 \leq n_{0i} \leq N \quad (n_{1,i-1} + n_{0i} = n_i),$$

where the first suffix indicates attachments to the tail and the second to any other position on the virus. We shall show that the $\{n_{1,i-1}\}$, $\{n_{0i}\}$ $(i = 1,\ldots,s)$ can be approximated by deterministic values, and also obtained stochastically using the previous deterministic approximation to $x(t)$. Loss of infectivity in the deterministic case results when all virus particles have acquired tail antibody attachments; in the stochastic case the probability

$$\Pr\{n_{0s} = 0,\ n_{01} = 0, \ldots, n_{0s-1} = 0\}$$

will give a measure of the non-infectivity. We now proceed to consider these cases in detail.

2. <u>The attachment pattern of antibody to virus</u>

Suppose we consider first a deterministic approximation to the attachment of antibodies to virus particles with s possible emplacements. For time $t \geq 0$, let the differentiable functions $u_0(t),\ldots,u_s(t)$ approximate the number of particles with $0,1,\ldots,s$ virus attachments, where

$\sum_i n_i(t) = N$; also let $x(t) = x_0 - \sum_i i n_i(t)$ be the antibodies remaining unattached at time t. Then if λ_i $(i = 1,\ldots,s;\ \lambda_s = 0)$ represents the attachment rate of a further antibody to a virus particle already carrying i of these, it is readily seen that

$$\frac{dn_0}{dt} = -\lambda_0 n_0 x,$$

$$(2.1)\qquad \frac{dn_i}{dt} = (\lambda_{i-1} n_{i-1} - \lambda_i n_i)x \qquad (i = 1,\ldots,s),$$

$$\frac{dx}{dt} = -x \sum_{i=0}^{s-1} \lambda_i n_i,$$

represent the state equations for the $\{n_i(t)\}, x(t)$. The initial conditions are

$$n_0(0) = N,\ n_i(0) = 0 \quad (i=1,\ldots,s),\ x(0) = x_0.$$

Writing (2.1) in matrix form, we obtain following the transformation $\rho(t) = \int_0^t x(\tau)\,d\tau$, that

$$(2.2)\qquad \frac{d\mathbf{n}}{d\rho} = -\mathbf{L}\,\mathbf{n}$$

where $\mathbf{n}' = (n_0, n_1, \ldots, n_s)$ denotes the row vector of the $\{n_i(t)\}$ and

$$(2.3)\qquad \mathbf{L} = \begin{bmatrix} \lambda_0 & & & & \\ -\lambda_0 & \lambda_1 & & & \\ & & \ddots & & \\ & & -\lambda_{s-2} & \lambda_{s-1} & \\ & & & -\lambda_{s-1} & \lambda_s \end{bmatrix}$$

If $\underset{\sim}{L}$ is written in the canonical form

$$\underset{\sim}{L} = \underset{\sim}{A}^{-1} \underset{\sim}{\Lambda}\, \underset{\sim}{A}$$

where $\underset{\sim}{\Lambda}$ is the diagonal matrix of eigenvalues $\lambda_0, \ldots, \lambda_s$, then it is readily shown that the solution to (2.3) is

$$\text{(2.4)} \qquad \underset{\sim}{n}(t) = e^{-\underset{\sim}{L}\rho(t)}\underset{\sim}{n}(0) = \underset{\sim}{A}^{-1}\, e^{-\underset{\sim}{\Lambda}\rho(t)}\, \underset{\sim}{A}\underset{\sim}{n}(0)$$

where $\underset{\sim}{n}'(0)$ is the row vector $(N, 0, \ldots, 0)$. The equation for $d\rho/dt$ in (2.1) becomes

$$\frac{d\rho}{dt} = -\kappa \underset{\sim}{\lambda}' \underset{\sim}{n}(t) = -\kappa \underset{\sim}{\lambda}' \underset{\sim}{A}^{-1} e^{-\underset{\sim}{\Lambda}\rho(t)} \underset{\sim}{A}\underset{\sim}{n}(0),$$

where $\underset{\sim}{\lambda}' = (\lambda_0, \ldots, \lambda_s)$, and this may be rewritten as

$$\text{(2.5)} \qquad \frac{d^2\rho}{dt^2} = -\frac{d\rho}{dt}\, \underset{\sim}{\lambda}' \underset{\sim}{A}^{-1} e^{-\underset{\sim}{\Lambda}\rho(t)} \underset{\sim}{\Lambda}\, \underset{\sim}{n}(0)$$

$$= -\frac{d\rho}{dt}\left\{\sum_{i=0}^{s} c_i\, e^{-\lambda_i \rho(t)}\right\},$$

the c_i being constant coefficients of $e^{-\lambda_i \rho(t)}$. The explicit solution of this second order differential equation would provide the complete values for the elements of the vector $\underset{\sim}{n}(t)$; however, such a solution cannot in general be found.

A particular case in which (2.5) can be solved was considered in a slightly different context by Yassky (1962). Yassky postulated a linear relationship for the attachment parameters of the type

$$\text{(2.6)} \qquad \lambda_i = \alpha(s - i) \qquad (\alpha > 0)$$

and found that the system then simplified considerably. From (2.1) and the relation $x_0 = x + \sum_{i=1}^{s} i n_i$, he obtained for $x(t)$ the differential equation

$$(2.7) \qquad \frac{dx}{dt} + x\sum_{i=0}^{s-1}\alpha(s-i)n_i = \frac{dx}{dt} + \alpha\{x - N(m-s)\}x = 0,$$

where $m = x_0/N > 1$ denotes the multiplicity of antibodies.

The solution to (2.7) is

$$(2.8) \qquad x(t) = \frac{x_0(s-m)}{s e^{\mu t} - m}$$

where $\mu = N\alpha(s-m)$, and from it, the solutions for the $n_i(t)$ are directly found to be

$$(2.9) \qquad \begin{aligned} n_0(t) &= N\{e^{-\mu t} + s(s-m)^{-1}(1-e^{-\mu t})\}^{-s}, \\ n_i(t) &= \binom{s}{i} n_0 \left\{\left(\frac{n_0}{N}\right)^{-s^{-1}} - 1\right\}^{i} \qquad (i = 1, \cdots, s-1), \\ n_s(t) &= N - \sum_{i=0}^{s-1} n_i(t). \end{aligned}$$

If we assume the attachment of antibodies to occur as a Markov process, it is simple to obtain the forward Kolmogorov equations for the probabilities $P(n_0, \ldots, n_s; x; t)$ that at time t, the viruses are partitioned into classes $\{n_i\}$ and there are x unattached antibodies. Although such equations (of birth process type) can be solved in principle, they prove to be rather intractable in practice, and a simplification is helpful. This consists in considering the

reduced stochastic process for which $x(t)$ is a deterministic differentiable function of t, while the $\{n_i\}$ are stochastic variables.

Let $\{\lambda_0, \ldots, \lambda_s\}$ be the set of attachment parameters such that $\lambda_i > 0$ $(i = 0, \ldots, s-1)$ but $\lambda_s = 0$. The probability of attachment in time δt of an antibody to a virus already carrying i phages is assumed to be

$$\lambda_i \, n_i \, x \, \delta t + o(\delta t),$$

where $n_i \geqslant 0$ is the discrete random number of bacteria having i attached phages $(i = 0, \ldots, s)$, and $x(t) = df/dt$ is the deterministic solution of equation (2.5).

Writing $Q = Q(n_0, n_1, \ldots, n_s\,;\,t)$ as the probability that at time $t \geqslant 0$ there are $n_0, \ldots, n_s$ viruses with respectively $0, \ldots, s$ attached antibodies, we find for the forward Kolmogorov equations

$$(2.10) \quad \frac{\partial Q}{\partial t} = \sum_{i=0}^{s-1} \lambda_i n_i x Q + \sum_{i=0}^{s-1} \lambda_i (n_i+1) x \, Q(n_0, \ldots, n_i+1, n_{i+1}-1, \ldots, n_s\,;\,t).$$

If $\Phi(u_0, \ldots, u_s; t)$ is the p.g.f. of these probabilities, then equations (2.10) lead to

$$(2.11) \qquad \frac{\partial \Phi}{\partial t} = \sum_{i=0}^{s-1} \lambda_i x \,(u_{i+1} - u_i)\, \frac{\partial \Phi}{\partial u_i}.$$

This is a particular case of the multivariate Markov process originally discussed by Bartlett (1949).

I was able to show (Gani 1965a) that for a general non-increasing function $x = x(t)$ for unattached phages, the partial differential equation (2.11) can be solved to obtain the p.g.f. explicitly as

$$\varphi(u_0, \ldots, u_s ; t) = \left\{ \sum_{i=0}^{s} u_i a_i(t) \right\}^N , \tag{2.12}$$

with probabilities

$$Q = \frac{N!}{n_0! \cdots n_s!} a_0^{n_0} \cdots a_s^{n_s} \tag{2.13}$$

of multinomial form, where the probabilities $a_i(t)$ are given by

$$a_i(t) = \sum_{j=0}^{i} B_{0j} A_{ji} e^{-\lambda_j \rho(t)} \quad (i = 0, \ldots, s) \tag{2.14}$$

with

$$B_{00} = 1 \quad , \quad B_{0j} = \prod_{r=0}^{j-1} \lambda_r (\lambda_r - \lambda_j)^{-1} \quad (j = 1, \ldots, s)$$

$$A_{ii} = 1 \quad , \quad A_{ji} = \prod_{r=j+1}^{i} \lambda_{r-1} (\lambda_r - \lambda_j)^{-1} \quad (j = 0, \ldots, i-1, \; i = 1, \ldots, s)$$

elements of the matrices $B = A^{-1}$, A respectively.

The expectations for this process are

$$E(n_i) = N a_i(t),$$

and the variances $Var(n_i)$ and covariances $Cov(n_i, n_j)$ $(i \neq j)$ are also easily obtained. If the λ_i take the special form (2.6) suggested by Yassky, then

$$\rho(t) = \int_0^t x(\tau) d\tau = \frac{1}{\alpha} \ln \left(\frac{s - m e^{-\mu t}}{s - m} \right) , \tag{2.15}$$

and the expectations $Ea_i(t)$ reduce to the expressions (2.9) found for the fully deterministic case.

3. The covering of spherical virus particles: loss of infectivity

The problem of covering a spherical virus particle by a sufficient number of cylindrical antibodies standing normally to its surface, thus preventing virus contact with healthy cells, has been outlined in Section 1. We saw that this was reducible to the geometrical problem of covering a sphere randomly by circular caps, each cap subtending a half angle $\hat{\alpha}$ at its centre.

Moran and Fazekas de St.Groth have pointed out in their paper (1962) that the problem is a generalisation of Stevens' (1939) random distribution of i arcs of length x on a circle of unit circumference, for which the asymptotic probability of coverage for large i is

$$(3.1) \qquad P(i) \sim i\,(1-x)^{i-1} .$$

Using extremely ingenious approximation methods, and assuming $\hat{\alpha} \leq 90^\circ$ to be small or of moderate size (as in the case where $\hat{\alpha} = 53.13^\circ$ for the sphere of radius 40 mμ, and an antibody of length 27 mμ), and the number of uncovered regions to follow a Poisson distribution, Moran and Fazekas de St.Groth obtained the asymptotic probability of coverage for large i as

$$(3.2) \qquad P(i) \sim \exp -\tfrac{1}{2}\pi^2 \left[\left\{ 2\left[\tfrac{1}{2}(1+\cos\hat{\alpha})\right]^{i} \left(1 + \frac{i^2}{\pi^2}\tan^2\tfrac{1}{2}\hat{\alpha}\right) \right\}^{-1} - 1 \right]^{-1} .$$

More recently Gilbert (1965) has derived for $\hat{\alpha} = 90^\circ$ the exact result

$$(3.3) \qquad P(i) = 1 - (i^2 - i + 2)2^{-i}$$

and has obtained quite generally for any angle $\hat{\alpha} \leqslant 90^\circ$ when $i > (\sin^2 \frac{1}{2}\hat{\alpha})^{-1}$ the bounds

$$(3.4) \qquad 1 - \tfrac{4}{3}\, i(i-1)(1-\sin^2\tfrac{1}{2}\hat{\alpha})^{i-1}\sin^2\tfrac{1}{2}\hat{\alpha} \leqslant P(i) \leqslant 1 - (1-\sin^2\tfrac{1}{2}\hat{\alpha})^{i},$$

for the probability $P(i)$ of coverage of the sphere.

These results together with a knowledge of the $\{n_i\}$ discussed in Section 2, allow us to consider changes in the loss of infectivity with time. For the case where the $\{n_i(t)\}$ are deterministic, we might for convenience count their values as

$$\begin{aligned} n'_i &= 0 \text{ if } n_i(t) < \tfrac{1}{2}, \\ n'_i &= j \text{ if } j-\tfrac{1}{2} \leqslant n_i(t) < j+\tfrac{1}{2} \qquad (j=1,\ldots,N-1), \\ n'_i &= N \text{ if } N-\tfrac{1}{2} \leqslant n_i(t) \leqslant N. \end{aligned}$$

In this case, the probability of loss of infectivity $Q_D(t)$ at time $t \geqslant 0$ will be given by

$$Q_D(t) = \prod_{i=0}^{S} [P(i)]^{n'_i}$$

where the n'_i are the values of the $n_i(t)$ counted as above.

Clearly, coverage of the virus is impossible for $i \leqslant r$, r being the minimum number of antibodies which can totally cover the sphere. Thus

for $i = 0,\ldots,r-1$, $P(i) = 0$. When $n'_0 = n'_1 = \cdots = n'_{r-1} = 0$, we have that $[P(i)]^0 = 1$, and thus

$$Q_D(t) = \prod_{i=r}^{s} [P(i)]^{n'_i} .$$

These results, though clearly approximate, will give some indication of the progressive loss of infectivity of the virus particles in time.

For the stochastic case, the probability of loss of infectivity $Q_S(t)$ is given by

$$
\begin{aligned}
(3.5) \quad Q_S(t) &= \sum_{\{n_i\}} \prod_{i=0}^{s} [P(i)]^{n_i} P(n_0,\ldots,n_s;t) \\
&= \sum_{\{n_i\}} [P(0)]^{n_0} \cdots [P(s)]^{n_s} \frac{N!}{n_0! \cdots n_s!} a_0^{n_0} \cdots a_s^{n_s} \\
&= [a_0 P(0) + \cdots + a_s P(s)]^N \\
&= [a_r P(r) + \cdots + a_s P(s)]^N ,
\end{aligned}
$$

where, in general, the $a_i(t)$ are those given in (2.13) and the $Na_i(t)$ reduce to (2.9) in the special case where we set $\lambda_i = (s-i)\alpha$.

We illustrate the preceding stochastic process by means of an elementary example. Let $\hat{A} = 90^\circ$, $N = 10$, $x_0 = 60$ ($n = 6$) $s = 5$, $\alpha = 1$; then $\mu = -10$, and

$$x(t) = \frac{60}{6 - 5e^{-10t}} .$$

It follows that the $\{a_i(t)\}$ are given by

$$
\begin{aligned}
a_0(t) &= E\,n_0(t)/N = (6e^{10t}-5)^{-5}\\
a_1(t) &= E\,n_1(t)/N = 5\,(6e^{10t}-6)(6e^{10t}-5)^{-5}\\
a_2(t) &= E\,n_2(t)/N = 10\,(6e^{10t}-6)^2(6e^{10t}-5)^{-5}\\
a_3(t) &= E\,n_3(t)/N = 10\,(6e^{10t}-6)^3(6e^{10t}-5)^{-5}\\
a_4(t) &= E\,n_4(t)/N = 5\,(6e^{10t}-6)^4(6e^{10t}-5)^{-5}\\
a_5(t) &= E\,n_5(t)/N = \left\{\frac{6e^{10t}-6}{6e^{10t}-5}\right\}^5 .
\end{aligned}
$$

Since r = 4 in this case, it follows from (3.5) that

$$
\begin{aligned}
Q_5(t) &= 5\,(6e^{10t}-6)^4(6e^{10t}-5)^{-5}\,P(4)\\
&\quad + \left\{\frac{6e^{10t}-6}{6e^{10t}-5}\right\}^5 P(5)\\
&= \frac{5}{9}\,(3-2e^{-10t})\,\frac{(6-6e^{-10t})^4}{(6-5e^{-10t})^5} .
\end{aligned}
$$

This provides some indication of the dependence on time of the loss of infectivity. Two remarks seem in order. First, it is clear that since for $\hat{\alpha} \neq 90^\circ$ the results given by Moran and Fazekas de St. Groth are asymptotic for large values of i, it is necessary for good approximations that the number s of emplacements be large. Secondly, while for simplicity in the model, we have allowed random attachment to the antibody in any position on the spherical virus surface, there are in fact only a fixed number of emplacements with specific positions on the spherical surface at which the antibody may adhere. In our example, taking $s = 5$, it is possible as $t \to \infty$ to reach the limiting probability $q_s = 5/16$ of non-infectivity. This would in practice be uselessly small. In fact if there were only 5 emplacements on the virus particle, total coverage would occur with probability 1 with 5 attachments. Thus, while the proposed model is not entirely unrealistic, it is at best a rough approximation to the true structure of the process.

4. Antibody attachment to the tail of a bacteriophage

Let us now suppose that the virus V is a bacteriophage, and that a single antibody attachment to its tail would prevent infectivity. We shall for simplicity consider the case where the general attachment parameter λ_i is of the form

$$\lambda_i = (s-i)\alpha \qquad (i = 0, 1, \ldots, s)$$

as in (2.6), though the subsequent methods apply quite generally for any $\lambda_i > 0$.

Considering either the deterministic or the stochastic case, we note that if tail attachments are not distinguished from attachments in other positions of the phage, then the $\{n_i(t)\}$ of (2.9) or the probabilities Q of (2.13) will fully describe the attachment process.

If, however, we wish to distinguish tail attachments from others, then we must concern ourselves with the classes

$$\begin{array}{ll} \{n_{00}\}, & \\ \{n_{0i}\}, \{n_{1,i-1}\} & (i=1,\ldots,s-1) \\ \{n_{1,s-1}\} & \end{array}$$

of bacteriophage with 0, i and s total attachments respectively, the first suffix position indicating a tail attachment. We see that

$$n_{00} = n_0, \quad n_{0i}+n_{1,i-1} = n_i, \quad n_{1,s-1} = n_s.$$

Let us first examine the deterministic case. Here, the attachment parameters associated with n_{00}, n_{0i} $(i=1,\ldots,s-1)$ are now in the form

TRANSITION	PARAMETER
$(0,0) \to (0,1)$ or $(1,0)$	$\lambda_0 = \alpha s$
$(0,i) \to (0,i+1)$	$\frac{(s-1-i)}{(s-i)}\lambda_i = \alpha(s-1-i)$
$(0,i) \to (1,i)$	$\frac{\lambda_i}{(s-i)} = \alpha$.

Thus we may write

$$\frac{dn_{00}}{dt} = \frac{dn_0}{dt} = -\alpha s N n_{00} ,$$

(4.1)
$$\frac{dn_{0i}}{dt} = \alpha(s-i)N\, n_{0,i-1} - \alpha(s-i)N\, n_{0i} \quad (i=1,\ldots,s-2),$$

$$\frac{dn_{0s-1}}{dt} = \alpha N\, n_{0s-2} - \alpha N\, n_{0s-1} ,$$

or in matrix form

(4.2)
$$\frac{d\mathbf{n}_0}{d\rho} = -\alpha \begin{bmatrix} s & & & \\ -(s-1) & (s-1) & & \\ & & \cdots & \\ & & -1 & 1 \end{bmatrix} \mathbf{n}_0 ,$$

where $\rho(t) = \int_0^t N(\tau)\, d\tau$ as before, and $\mathbf{n}_0' = (n_{00}, \ldots, n_{0s-1})$.

Using methods similar to those of Section 2, the solution of this set of differential equations is easily found to be

(4.3)
$$n_{0i}(t) = N \binom{s-1}{i} e^{-(s-i)\alpha\rho} \left(1-e^{-\alpha\rho}\right)^{i} \quad (i=0,\ldots,s-1),$$

where $\rho(t) = \frac{1}{\alpha} \ln\left\{\frac{s-me^{-\mu t}}{s-m}\right\}$ as in (2.15). It follows therefore, since

$$n_{00}(t) = n_0(t) = N\left\{e^{-\mu t} + s(s-m)^{-1}\left(1-e^{-\mu t}\right)\right\}^{-s}$$

as before, that the numbers of phage with tail attachments are

$$n_{1,i-1}(t) = n_i(t) - n_{0i}(t)$$

(4.4)

$$= \binom{s-1}{i-1} n_0 \left\{ \left(\frac{n_0}{N}\right)^{-s^{-1}} - 1 \right\}^{i} \qquad (i = 1, \ldots, s-1),$$

$$n_{1,s-1} = n_s = N - \sum_{i=0}^{s-1} n_i = N - \sum_{i=0}^{s-1} \binom{s}{i} n_0 \left\{ \left(\frac{n_0}{N}\right)^{-s^{-1}} - 1 \right\}^{i}.$$

Immunity may be considered to exist if all phage have a tail antibody attachment, that is if $\sum_{i=1}^{s} n_{1,i-1} = N$, or, since the $n_{1,i-1}(t)$ are not integers, when

$$(4.5) \qquad N - \sum_{i=1}^{s} n_{1,i-1} = \sum_{i=1}^{s} n_{0,i-1} = N e^{-\alpha\rho(t)} = N \frac{(s-m)}{(s-me^{-\mu t})} < \frac{1}{2}.$$

In the stochastic case, if we write

$$R = R(n_{00}, n_{01}, \ldots, n_{0s-1}; n_{10}; t) \qquad \left(n_{10} = N - \sum_{i=0}^{s-1} n_{0i}\right)$$

as the probability that there are at time t, n_{00}, n_{01}, $\ldots$, n_{0s-1} phages with $0, \ldots, s-1$ attachments respectively at other than tail positions, then assuming for $x(t)$ the deterministic solution (2.8), we have that

$$(4.6) \qquad \frac{dR}{dt} = \sum_{i=0}^{s-1} \alpha(s-i-1)(n_{0i}+1)x\, R(n_{00}, \ldots, n_{0i}+1, n_{0i+1}-1, \ldots, n_{0s-1}; n_{10}; t)$$

$$+ \sum_{i=0}^{s-1} \alpha x(n_{0i}+1)\, R(n_{00}, \ldots, n_{0i}+1, n_{0i+1}, \ldots, n_{0s-1}; n_{10}-1; t)$$

$$- \sum_{i=0}^{s-1} \alpha(s-i) n_{0i} x\, R(n_{00}, \ldots, n_{0s-1}; n_{10}; t).$$

The generating function for these probabilities $\psi(u_{00},\ldots,u_{0s-1};v;t)$ satisfies the partial differential equation

$$(4.7)\qquad \frac{\partial\psi}{\partial t} = \sum_{i=0}^{s-1}\alpha x\{(s-i-1)u_{0i+1}+v-(s-i)u_{0i}\}\frac{\partial\psi}{\partial u_{0i}}\,.$$

We may write in the usual way that

$$\frac{dt}{-1} = \frac{d\psi}{0} = \frac{dv}{0} = \frac{du_{00}}{\alpha x[(s-1)u_{01}+v-su_{00}]} = \cdots = \frac{du_{0s-1}}{\alpha x[v-su_{0s-1}]}$$

so that if $\underset{\sim}{U}' = (u_{00},\ldots,u_{0s-1})$, then

$$(4.8)\qquad \frac{d\underset{\sim}{U}}{dt} = \alpha x\begin{bmatrix} s & -(s-1) & & \\ & (s-1) & -(s-2) & \\ & & \cdots & \\ & & & 1\end{bmatrix}\underset{\sim}{U} - \alpha x\underset{\sim}{1}v$$

$$= \alpha x\,(\underset{\sim}{L}\,\underset{\sim}{U} - v\,\underset{\sim}{1})\,.$$

Treating v as a constant, the solution of this is seen to be of the form

$$e^{-\alpha\rho(t)\underset{\sim}{L}}(\underset{\sim}{U} - v\underset{\sim}{L}^{-1}\underset{\sim}{1}) = \text{Constant},$$

and it follows that

$$\psi(u_{00},\ldots,u_{0s-1};v;t) = \Psi(e^{-\alpha\rho(t)\underset{\sim}{L}}(\underset{\sim}{U}-v\underset{\sim}{L}^{-1}\underset{\sim}{1}),v)$$

subject to the condition that $\psi(u_{00},\ldots u_{0s}:v:0) = u_{00}^{N}$.

Thus

$$\Psi(\underset{\sim}{U} - v\underset{\sim}{L}^{-1}\underset{\sim}{1},v) = u_{00}^{N}$$

so that since $\underset{\sim}{L}^{-1}\underset{\sim}{1} = \underset{\sim}{1}$ for the matrix $\underset{\sim}{L}$ in (4.8),

$$(4.9)\qquad \Psi(e^{-\alpha\rho(t)\underset{\sim}{L}}(\underset{\sim}{U}-v\underset{\sim}{L}^{-1}\underset{\sim}{1}),v) = \{(e^{-\alpha\rho(t)\underset{\sim}{L}}(\underset{\sim}{U}-v\underset{\sim}{1}))_0+v\}^{N},$$

where $\left(e^{-\alpha \rho(t) \underset{\sim}{L}} (\underset{\sim}{U} + v \underset{\sim}{L}^{-1} \underset{\sim}{1})\right)_0$ indicates the 0-th element of the column vector.

It may readily be shown after some matrix calculations that the p.g.f. is of the form

$$(4.10) \quad \psi(u_{00}, \ldots, u_{s0}; v; t) = \left\{ \sum_{i=0}^{s-1} u_{si}\, b_i(t) + \left[1 - \sum_{i=0}^{s-1} b_i(t)\right] v \right\}^N,$$

where the $b_i(t)$ are of the form

$$(4.11) \quad \begin{aligned} b_0(t) &= e^{-s\alpha\rho(t)} = \left\{ e^{-\mu t} + s(s-m)^{-1}(1-e^{-\mu t}) \right\}^{-s} \\ b_i(t) &= \binom{s-i}{i} e^{-(s-i)\alpha\rho(t)} \left(1 - e^{-\alpha\rho(t)}\right)^i \\ & (i = 1, \ldots, s-1). \end{aligned}$$

These probabilities add up to

$$(4.12) \quad \sum_{i=0}^{s-1} \binom{s-1}{i} e^{-(s-i)\alpha\rho} \left(1 - e^{-\alpha\rho}\right)^i = e^{-\alpha\rho(t)}.$$

Thus for phage virus, the probability of loss of infectivity is given by

$$(4.13) \quad \left(1 - e^{-\alpha\rho}\right)^N = \left\{ \frac{m(1-e^{-\mu t})}{s - m e^{-\mu t}} \right\}^N.$$

5. Conclusion

Further investigations of more realistic models and their verification in the laboratory would be of interest. In the case of the influenza virus, for example, it is known that antibodies may bend over to attach both their ends to emplacements on the same virus particle. It is also possible for one end of an antibody to be attached to an emplacement

on one virus, while its other end is attached to a second virus particle; conglomerations of viruses and antibodies can thus be formed. Clearly, the geometry of such models becomes more complicated than that we have outlined earlier.

It may still be possible, however, to construct simplified models for them, and to draw probabilistic conclusions from these. Similarly, for bacteriophage, a model could be constructed in which antibodies have one end attached to the tail of one phage particle while the other is attached to a second phage tail. Such a model is not too intractable, and it is hoped to present results relating to it in some work at present in preparation.

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13. ABSTRACT

Several interesting mathematical problems concerned with partition into classes, and surface covering are suggested by the physical mechanisms and geometry of antibody attachment to virus particles. This paper outlines some of the recent work done in this area by Yassky (1962), the author (1965a,and b), Moran and Fazekas de St.Groth (1962) and Gilbert (1965), adds a model and other extensions of the author, and concludes with a suggestion for further investigations. The author has endeavoured throughout to hold the mathematical argument at a simple level, and to emphasize the model-building aspect of the work, in the hope that virologists may be tempted to use and perhaps verify experimentally some of the models put forward.

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